

### REMARKS/ARGUMENTS

#### **Claim Rejection - 35 USC § 103**

The examiner's reading of the primary reference, Winchell et al. US 5,874,573, is once again respectfully traversed. A chelation complex is a complex formed between a chelating agent that contains two or more electron donor atoms and a single metal atom by way of coordinate bonds between each of the electron donor atoms and the metal atom. This is distinct from a metal salt of an acid since the attraction between the metal and the acid is an electrostatic interaction rather than a coordination bond. An explanation of coordination bonds can be found in the definition of "coordination compound" in *Hawley's Condensed Chemical Dictionary*, Fourteenth Edition, John "Wiley & Sons, Inc. (2001):

**coordination compound.** (complex compound). A compound formed by the union of a metal ion (usually a transition metal) with a nonmetallic ion or molecule called a ligand or complexing agent. The ligand may be either positively or negatively charged (such ions as  $\text{Cl}^-$  or  $\text{NH}_2\text{NH}_3^+$ ), or it may be a molecule of water or ammonia. The most common metal ions are those of cobalt, platinum, iron, copper, and nickel, which form highly stable compounds. When ammonia is the ligand, the compounds are called amines. The total number of bonds linking the metal to the ligand is called its coordination number. It is usually 2, 4, or 6 and often depends on the type of ligand involved. All ligands have electron pairs on the coordinating atom (e.g., nitrogen) that can be either donated to or shared with the metal ions. The metal ion acts as a Lewis acid (electron acceptor) and the ligand as a Lewis base (electron donor). The bonding is neither covalent nor electrostatic but may be considered intermediate between the two types. The charge on the complex ion is the sum of the charges on the metal ion and the ligands; for example,  $4\text{NH}_3 + 2\text{Cl}^- + \text{Co}^{3+}$  forms the complex  $[\text{Co}(\text{NH}_3)_4\text{Cl}_2]^+$ . The brackets enclose the metal ion and the coordinated ligands. See chelate; sequestration; metallocene. (Emphasis added)

The only disclosure of calcium in Winchell et al. is calcium chloride that is present in admixture with the chelators to form calcium salts, not chelates of the ligand with calcium.

As regards the Weglicki et al. reference, US 5,854,287, the notion that any compound known to be an antioxidant will be effective against cardiovascular and neurological diseases is not justified by the disclosure of this reference. Over 4000 antioxidants have been identified, the best known of which are vitamin E, vitamin C, and the carotenoids. McGee SA et al. in "What Advanced Practice Nurses Need to Know About Free Radicals," *The Internet Journal of Advanced Nursing Practice*, ISSN 1523-6064, vol. 6, no. 1 (2003), state that

"Cardiovascular disease and cancer risk reduction are associated with diets rich in fruits and vegetables. The antioxidants present in these foods may be responsible for this protective effect. However, it has been difficult to isolate the antioxidant properties as the sole mechanism. Antioxidant supplementation is controversial. There are numerous opinions, but no definite answers in the literature."

Likewise, Bagchi K et al. in "Free radicals and antioxidants in health and disease," *Eastern Mediterranean Health Journal*, vol. 4, issue 2, pages 350-360 (1998), state that

"Whether vitamin E levels in normal diets are protective against heart disease still remains to be verified. Further research is needed to confirm the role of vitamin E, as well as to determine the optimal intake to protect against cardiovascular risk. ... The role of antioxidants in slowing the progression of certain neurological disorders has been suggested as oxidation may be a causative factor in several disorders of the nervous system. Supplementation with vitamin C and E might be of benefit in slowing the progression of Parkinson's disease. Further trials, however, need to be conducted to substantiate these claims."

(Emphasis added in both quotes) Both of these papers can be downloaded from the internet -- <http://www.ispub.com/ostia/index.php?xmlFilePath=journals/ijanp/vol6n1/radicals.xml> (McGee et al.) and <http://www.euro.who.int/Publications/EMHJ/0402/21.htm> (Bagchi et al.).

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The above quotes confirm that there is considerable uncertainty in the state of the art, and no assurance that antioxidants in general are effective against cardiovascular and neurological diseases. In view of this uncertainty, any suggestion from Weglicki that all antioxidants are effective against cardiovascular and neurological diseases is nothing more than speculation and not a sound basis for rejection of the patentability of particular antioxidants. This is particularly true in view of the lack of any chemical similarity between the D-propranolol

of Weglicki, which is neither a chelating agent nor a chelation complex, and the dihydroxyphosphorylalkyl triazacyclononanes addressed by the present invention. Winchell et al. and Weglicki in combination do not suggest the discovery that Applicant has made of the unusual activity of the compounds presently claimed.

Once again, and particularly with the reduction in claim scope achieved by the amendment herein, the nonobviousness and hence the patentability of the present invention is established by the improvement in performance shown by the comparative test data presented in the specification. As explained in the remarks accompanying Applicant's Amendment No. 1, Example 7 of the specification shows that the complex of the chelator with calcium and sodium and the complex of the chelator with magnesium and sodium were both superior in performance to the complex with sodium only, and the complex that contained calcium demonstrated an additional improvement over the complex that contained magnesium. These improvements are not suggested by any part of the disclosure in Winchell et al. 5,874,573, nor any part of the disclosure in Weglicki 5,854,287.

### ***Double Patenting***

The rejection of claims 2-12, 14, 18, and 21-26 over Winchell et al. US 5,874,573 for double patenting is once again respectfully traversed. The reduction in scope achieved by the above amendment is made in response to the Examiner's remarks and addresses this rejection. In view of this reduction in scope, the unexpected improvement in biological activity of chelators when administered as complexes with dicationic metals (such as calcium and magnesium) rather than monocationic metals (such as sodium) provides particularly strong support for the claims. As previously explained, the complexes with dicationic metals are a subset of the larger class claimed by Winchell et al. '573, and are indeed patentably distinct, as Applicant's experimental data attests. The artisan would have no way of knowing that complexes with dicationic metals would have any special benefit and would not be motivated to select these over any other complexes in the Winchell et al. '573 class. Accordingly, the present claims are not obvious over those of Winchell et al. '573.

**CONCLUSION**

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance, and reconsideration of all outstanding rejections is respectfully requested. Should any matters remain that can be resolved by a telephone conference with Applicants' attorney, the Examiner is encouraged to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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